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The Neuroprotective Role of Vesicular Monoamine Transporter 2 in Neurodegenerative Diseases

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Abstract: Neuropharmacological relation of religious belief supports the role of dopaminergic activation as the leading neurochemical feature. However, vesicular monoamine transporter-2 (VMAT-2) has been shown to be responsible for removing of neurotransmitters such as dopamine that may secondarily lead to a neuroprotective activity by different neurodegeneration models. Moreover, there are interesting data showing that VMAT-2 may play an important role during religious belief and experience. In the light of these findings, we aimed to review the preclinical and clinical neuroprotective data of Vesicular monoamine transporter (VMAT-2) in different neurodegenerative and neuropsychiatric diseases. In respect of rapidly increasing evidences about the neurobiological and neuroimaging correlates of religious belief, we hypothesized that there is a link between belief and neuroprotection.

Keywords: VMAT-2, neuroprotection, religious belief.

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1. INTRODUCTION

Religiosity is a broad, comprehensive and sociological term that include numerous aspects of religious activity, experience and belief. However, although religious practices and belief are universal throughout human history the difference between believing and disbelieving a proposition is one of the most important factors influencing the human emotion [1-3,68]. Current neuropsychological and functional imaging findings studies suggest neo-striatal, limbic, and prefrontal cortical networks as critical areas in the widely distributed neural networks that clearly support common religious practices such as prayer and meditation [1-11]. However, despite strong evidences supporting the psychoprotective role of religious belief it is still unclear whether religious belief can exert a neuroprotective effect [12-15]. Recent studies indicated that the religious belief can provide significant protective effect for the development of depression, suicidality, emotional stress and anxiety disorder [12-15]. Additionally, despite different effects of religious belief on the progression of AD and MCI [18], that can be related to the distinct neuropathological presentations and development of AD or smaller sample of AD cases, higher levels of spirituality and private religious practices have been shown to be associated with slower progression of Alzheimer disease, lower risk of mild cognitive impairment and a higher quality of life in patients with Amyotrophic lateral sclerosis (ALS) [16-19]. Moreover, it has been shown that the strength of religious beliefs acts as a possible protective factor against post-stroke emotional distress [15]. Neuropharmacological correlates of religious belief indicate to dopaminergic activation as the-leading neurochemical feature which involves mainly the ventral dopaminergic pathways [20]. In addition to increased brain GABA levels and decreased cortisol levels by meditation practitioners, personality trait covering religious behavior and attitudes have been shown to be associated with serotonin 5-HT(1A) receptor density on the dorsal raphe nuclei, the hippocampal formation, and the neocortex [21-23]. Borg et al showed by their interesting study that scores for spiritual acceptance versus material rationalism correlated significantly with 5-HT1A binding potential in specified brain regions and suggested a biological underpinning for the variability in religious behavior in humans that is specifically related to the central serotonergic system [23]. This was in accordance with previous studies showing that clinical personality test scores including the novelty seeking and harm avoidance scales are linked to variations in the dopamine D4 receptor and serotonin transporter gene [24-27] suggesting a strong link between the neurotransmitter receptor distribution and temperament dimensions of personality. In the light of these findings we aimed to explore the neuroprotective role of newly defined vesicular monoamine transporter which has been recently hypothesized to play a critical

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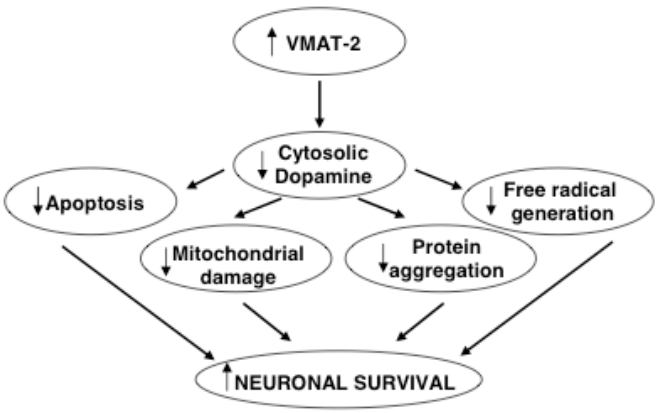

Fig. (1). The neuroprotective effect of VMAT 2.

physiological role by producing mystic sensations including the presence of God [27].

2. VESICULAR MONOAMIN TRANSPORTER 2 (VMAT 2) IS A POSSIBLE NEUROPROTECTIVE AGENT ?

It is widely known that neurotransmitters and their transporting mechanism play an important role in the control of programmed cell death in the brain. Vesicular monoamine transporters (VMATs) are vesicular membrane-spanning proteins and belong to the members of the toxinextruding antiporter family. They are responsible for the packaging of neurotransmitters (such as dopamine, serotonin, norepinephrine, and epinephrine *via* a proton electrochemical gradient) into synaptic vesicles and also translocate toxicants away from cytosolic sites of action also including 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [28]. VMAT2 is primarily expressed in adult human and rodent monoaminergic neurons of the central nervous system and sympathetic postganglionic neurons [29]. Although the highest levels of VMAT have been found in the striatum in human studies, recent human studies showed the expression of VMAT 2 also in the extrastriatal regions which have been shown to be activated during the religious experience [30, 31]. VMAT 2 differs from VMAT 1 with its unique transporting activity on the cytoplasmic dopamine (DA) moving the cytoplasmic dopamine for storage and subsequent exocytotic release into synaptic vesicles [29, 32]. Thus in the case of dopamine, VMAT2 is responsible for removing the dopamine from the cytosol where it can be more readily oxidized and package it into vesicles for the neurotransmission as a next step. In this respect, the majority of preclinical studies showed the neuroprotective activity of VMAT 2 mainly by the parkinsonian neurodegeneration models where the cytosolic metabolism and related formation of reactive oxygen species of dopamine may play an important role by the loss of nigrostriatal DA neurons [29, 33-43]. Additionally, VMAT 2 has been also shown to sequester 1-methyl-4-phenylpyridinium (MPP+) in synaptic vesicles and to protect catecholamine-containing neurons from MPP+ -induced toxicity and degeneration [29, 44-48]. This was suggested by other studies using heterozygous VMAT2 knockout mice showing that the knockouts are more vulnerable to the neurotoxic effects of MPTP, methamphetamine and L-3,4 dihydroxyphenylalanine [29, 49-51]. The latter results support that reduction in VMAT2 activity might attenuate the efficacy of L-DOPA therapy also in Parkinson's patients, and pharmacological agents that increase VMAT 2 activity could exert a neuroprotective effect [29, 52]. Interestingly, recent studies have shown that regulatory polymorphisms in VMAT2 affecting its quantitative expression might serve as a genetic risk factors for Parkinson's disease [53-55]. In accordance with this, methylphenidate, pramipexole and apomorphine have suggested protection against the loss of nigrostriatal DA *via* their increasing effect on VMAT2 activity that finally increases the vesicular DA uptake [29, 56-61]. Moreover, a genetic animal model for clinical depression in humans, suggest that alterations in VMAT 2 may also play a role in the etiology of depression [62], and recent studies suggested that VMAT 2 may also play an important role in the development of nicotine and alcohol dependence [66,67]. Taken together, the results of the above studies indicate that VMAT2 expression and function are important in restricting the neurotoxicity of environmental and endogenous neurotoxins that play an etiologic role in neurodegenerative as well as neuropsychiatric diseases.

3. INTERESTING EVIDENCE FOR THE LINK BETWEEN SPIRITUALISM, VMAT-2 AND NEURODEGENERATIVE DISEASE: A FOCUS ON PARKINSON'S DISEASE

After Dr Hamer analyzed DNA and personality score data from over 1000 individuals and identified one particular locus, VMAT 2, with a significant correlation with religious belief, a following small size study showed statistically insignificant but higher average self-transcendence score for the genetically spiritual than the nonspiritual group (18.5 possible points versus 12.5) [27, 63]. Although this statistical data can be attributed to the limited power of statistical testing in small samples these studies suggest an important genetic and neurobiological correlate of spiritualism and opens an interesting window showing that VMAT may serve as a possible link between belief and neuroprotection especially with its recently defined expression on the brain regions which are also involved during religious experience. It has been already shown that VMAT 2 can protect against psychiatric and neurological disorders which are characterized with neuronal cell loss. However, with its expression limited only in striatal regions, it is still obscure how VMAT 2 can exert a neuroprotective effect by neuropsychiatric diseases that are characterized with widely distributed neuronal cell loss. In previous studies, positron emission tomography (PET) imaging with the VMAT2 tracer 11C-dihydrotetrabenazine (11C-DTBZ) has been proven to be an objective marker of nigrostriatal terminal integrity [69]. However a recently developed novel tracer 18F-9-fluoropropyl-(+)-dihydrotetrabenzazine(18F-FP-(+)-DTBZ) for VMAT 2 imaging with a longer half-life [3] has been also shown to exert high sensitivity for detecting dopaminergic integrity in both healthy subjects and PD patients [70-73]. Thus, Lin et al have recently investigated the *in vivo* VMAT2 distribution in the human brain, using 8F-FP-(+)-DTBZ PET radiotracer by 22 healthy subjects and found that the VMAT 2 protein was not only distributed in the usual nigrostriatal pathways, but also the mesolimbic, mesocortical pathways, serotonin and norepinephrine pathways [30].

These *in vivo* imaging characteristics of VMAT 2 displayed similar distribution patterns to the *in vitro* VMAT 2 protein levels reported in a recent autopsy study and are also consistent with other studies focused on the overall brain distribution of VMAT 2 proteins [30, 31]. Regarding the evidences suggesting the role of dopamine as a principal neuropharmacological correlate of religious belief and the strong expression of VMAT2 on striatal regions it is an interesting issue to evaluate relationship between VMAT 2 expression, religious belief and clinical progression by PD patients. Thus, McNamara et al quantitatively explored the neuropsychological and neuropsychiatric correlates of religiosity in Parkinson's disease (PD) patients and found that patients with PD reported significantly lower levels of religiousness that was related primarily to a measure of prefrontal neuropsychological function [64]. This was suggested by recent reports showing that measures of "self-transcendence" correlated well with genetic markers for the dopamine transport molecule which is strongly determined in the prefrontal cortex [63-65]. Beyond suggesting the functional significance of VMAT 2 by extrastriatal regions, these studies open a new window suggesting that VMAT polymorphism can serve as a genetic risk factor for Parkinsons disease. In this respect studies evaluating the relationship between the genetic variants in VMAT 2 gene and the susceptibility of the PD found that variability within the VMAT 2 promoter region and haplotypes may reduce the risk of developing PD. Thus Glatt et al showed by their population based study that 2 polymorphisms located in the putative promoter region of the VMAT 2 gene were inversely associated to PD, whereas the other single-nucleotide polymorphisms (SNPs) within the gene were not related to the risk of developing PD. Moreover, in another human study a high degree of genetic variability and the associated affection of the mechanisms of nigrostriatal degeneration has been shown in the promoter region of SLC18A2, which is a gene for VMAT 2 that is located on chromosome 10q25 and is a candidate gene for Parkinson Disease (PD) [53,54]. This suggests that striatal VMAT 2 expression by PD patients may exert a neuroprotective effect which may interact with religious belief that should prompt us to evaluate whether there is an association between the quantitative VMAT 2 expression and religiosity by PD patients. However based on recent evidences showing that the neuroprotective effect of dopamine agonists and free radical scavengers are associated with the redistribution of VMAT 2 that is associated with the down-regulating of apoptotic pathways, mitochondrial damage and toxic protein aggregation in the dopaminergic neurons [74-79], it can be hypothesized that VMAT 2 may serve as a potential target for the treatment of several neurodegenerative disorders involving the dopaminergic system [74-79].

4. CONCLUSION

VMAT 2 seems to be an interesting neuroprotective candidate in neurodegenerative diseases. However, recent studies suggested that the VMAT 2 can be associated with religious experience in various brain regions. Herein, we reviewed the comprehensive explanation of VMAT expression under specific circumstances and its relation to the neuroprotective findings in religious experience. Besides its well-known striatal expression, it can be hypothesized that the VMAT expression may be increased under spiritual experiences especially on the predefined religion related brain regions which may in turn lead to a neuroprotective effect. Thus exploring the distribution of VMAT2 on the extrastriatal regions may not only help in clinical evaluation of many neuropsychiatric disorders that involved these monoaminergic systems but may also provide a strong evidence for a correlation between spiritual experience and the quantitative amounts of VMAT 2 protein in the religion related areas. In this respect, according to our opinion, VMAT 2 PET imaging before and after spiritual exercises with correlated clinical transcendence scores and baseline VMAT genotype analysis can be a sophisticated approach quantitatively to explore neuropsychiatric correlates of VMAT 2.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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